Respiratory Medicine (2010) **104**, 1344–1349

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Intrathoracic manifestations of Rosai–Dorfman disease

Rodrigo Cartin-Ceba [a], Jason M. Golbin [b], Eunhee S. Yi [c], Udaya B.S. Prakash [a], Robert Vassallo [a,d,*]

[a] *Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200, First Street SW, Rochester, MN 55905, USA*
[b] *Long Island Lung Center, Bay Shore, NY, USA*
[c] *Division of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA*
[d] *Clinical Immunology and Immunotherapeutics Program, Mayo Clinic, Rochester, MN 55905, USA*

Received 2 November 2009; accepted 27 March 2010
Available online 24 April 2010

KEYWORDS
Rosai–Dorfman disease;
Interstitial lung disease;
Histiocyte;
Lymphadenopathy;
Macrophage;
Chest CT

Summary
Introduction: Rosai–Dorfman Disease (RDD), also known as Sinus Histiocytosis with Massive Lymphadenopathy (SHML), is a rare monocyte/macrophage proliferative disorder of varied biological behavior. Although cutaneous and lymph node involvement are relatively well-described, intrathoracic manifestations of RDD have only occasionally been reported.
Methods: We conducted a retrospective computer-assisted search of the Mayo Clinic record from 1976 to 2005 for patients with histopathologic evidence of RDD on organ biopsy. Clinical characteristics were abstracted from charts and thoracic manifestations recorded. Survival was estimated using the national social security database.
Results: A total of 21 patients were diagnosed with RDD over a period of 30 years; 9 had intrathoracic manifestations (43%). Main pulmonary symptoms included dyspnea and cough. Age at the time of diagnosis, gender, race, smoking history, mortality and time of survival after diagnosis were no different between RDD patients with and without intrathoracic manifestations. The most common radiographic thoracic manifestation was mediastinal lymphadenopathy (6 patients). Cystic change, interstitial lung disease, and airway disease were radiographically evident in 4 patients. Seven patients were treated at some point in the course of their disease, most commonly with oral corticosteroids. At the time of last follow-up 87% were alive, with a median (IQR) time interval since diagnosis of 8 years (4–9.7).
Conclusions: Intrathoracic manifestations of RDD are relatively common and include mediastinal lymphadenopathy, airway disease, pleural effusion, cystic and interstitial lung disease. Although limited in size, this series suggests the prognosis of patients with RDD and intrathoracic manifestations is relatively good.

* Corresponding author. Tel.: +1 507 284 5398.
E-mail address: Vassallo.robert@mayo.edu (R. Vassallo).

0954-6111/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.03.024

Introduction

In 1969, Rosai and Dorfman described a series of individuals with a non-malignant lymphohistiocytic proliferative condition predominantly involving lymph nodes and clinically resulting in painless lymphadenopathy.[1] In a later publication, 30 additional cases of this unique condition were described, resulting in the establishment of sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai—Dorfman disease (RDD), as a clinicopathologic entity.[2] Other lymphatic groups, such as mediastinal, axillary and inguinal lymph nodes can also be involved, and in approximately 25—40% of cases, extranodal sites are affected.[3—5] Extranodal involvement is often responsible for the more clinically significant manifestations of the disease.[6] Although sporadic cases of thoracic RDD have been reported in the literature,[3,7—9] the clinical and radiological characteristics, progression, therapy and survival of RDD patients with predominantly intrathoracic involvement have not been well defined. In this retrospective study, the clinical and radiological findings, as well as therapy and outcomes of a cohort of patients with RDD and intrathoracic manifestations are described.

Methods

The Mayo Clinic Institutional Review Board approved the study protocol. A retrospective computer-assisted search of the Mayo Clinic records from 1976 to 2005 for patients with histopathologic evidence of RDD on organ biopsy was performed. Individuals with an unequivocal histopathological diagnosis of RDD were included. Clinical characteristics were abstracted from paper and electronic medical records and intrathoracic manifestations recorded. All radiological images were reviewed by three of the authors (RCC, RV and JMG). Survival was assessed utilizing the national social security database. Clinical characteristics were compared between RDD subjects with intrathoracic manifestations and RDD subjects without intrathoracic manifestations.

Statistical analysis: All continuous data are summarized as medians (interquartile range, IQR). Categorical data are summarized as percentages. Difference in medians between groups was tested with the Wilcoxon sum rank test. Differences in proportions were compared utilizing the chi-squared test or the Fisher exact test as appropriate. Death was determined from the state and national death index. JMP 8.0 software was utilized for analysis of the data. For all statistical tests, a 2-tailed P value of <0.05 was considered statistically significant.

Results

A total of 21 patients were diagnosed with RDD over a period of 30 years at our institution; 9 (43%) had evidence of intrathoracic RDD. Table 1 presents the comparison of the clinical characteristics between RDD subjects with intrathoracic manifestations and RDD subjects without. There were no significant differences between the two groups in age at the time of diagnosis, gender, race, smoking history, mortality or time of survival after diagnosis (Table 1). Clinical and radiographic characteristics of patients with intrathoracic RDD are summarized in Table 2. In patients with intrathoracic RDD manifestations, the most common respiratory symptoms included dyspnea in 8 patients and cough in 5. Only two smokers were identified. Pulmonary function tests were only available for 3 patients, one of which was normal; the other 2 studies demonstrated moderate restrictive physiology and low diffusing capacity of the lung for carbon monoxide (DLCO) in 1 patient, and mild obstructive physiology with normal DLCO in the last patient.

The most common intrathoracic manifestation of RDD was mediastinal lymphadenopathy in 6 patients (66%). The most common extrathoracic manifestation among patients with intrathoracic RDD was cervical lymphadenopathy in 6 patients (66%). Four patients (44%) presented to clinical attention primarily because of respiratory tract disease; the main imaging findings in these 4 cases were cystic lung disease, airway disease (air trapping and bronchiectasis), pleural effusion with mediastinal adenopathy (Fig. 1), and interstitial lung infiltrates in two patients (Fig. 2). Fig. 2 illustrates the radiological findings in one of the patients with interstitial pulmonary infiltrates. The diagnosis of RDD with interstitial lung infiltrates was established in two patients following identification of typical features of RDD on surgical lung biopsy (Fig. 3). Seven patients received pharmacotherapy during the course of their disease, most commonly with oral corticosteroids. The 2 patients not treated with corticosteroids remained stable during the follow up period. The majority of patients demonstrated subjective clinical improvement after therapy with steroids (6 patients), and one patient (patient #9) experienced a decline in a one-year follow-up pulmonary function testing showing a severe restrictive pattern. This patient developed worsening oxygenation and was evaluated for lung transplantation at another academic institution. At the time of last follow-up, all patients except one were still alive, for a median (IQR) survival of 8 years (4—9.7) after diagnosis. All three fatalities in the cohort were non-RDD related (cardiovascular events).

Discussion

In this retrospective cohort of 21 adult patients with biopsy-proven RDD identified over a period of 30 years at a tertiary care institution, we report that a significant proportion of patients develop intrathoracic involvement. In addition, we have identified mediastinal lymphadenopathy as the most common intrathoracic manifestation of RDD. The current study also reports the occurrence of RDD as an interstitial pulmonary process with radiographic features that are similar to those reported in idiopathic interstitial pneumonias. The disease follows a relatively benign course in most patients and the occurrence of intrathoracic involvement with RDD does not seem to portend a worse prognosis compared to other patients without thoracic involvement.

RDD is a disorder characterized by non-malignant proliferation of distinctive histiocytic/phagocytic cells primarily within lymph node sinuses and lymphatics in extranodal sites.[3,10] The histiocytic disorders are classified according to the presumed cell of origin. Langerhans cell Histiocytosis (LCH) and RDD are both disorders of varied biological behavior originating from abnormally

Table 1 Clinical characteristics of Rosai—Dorfman disease patients with and without intrathoracic manifestations.

	Intrathoracic manifestations $N = 9$	No intrathoracic manifestations $N = 12$	P value
Age at diagnosis (years) median, IQR	45 (23—50)	53 (35—68)	0.24
Female gender, *N* (%)	5 (56)	8 (67)	0.67
Caucasians, *N* (%)	8 (89)	9 (75)	0.60
Prior smoking history, *N* (%)	2 (22)	1 (8.3)	0.55
Mortality, *N* (%)	1 (11)	2 (17)	0.99
Time alive after diagnosis (years), median (IQR)	8 (4—9.7)	7.9 (4.9—14.8)	0.77

N = Number, IQR: Interquartile range.

proliferating histiocytic cells; however, LCH and RDD are clinically distinct entities. While LCH is a dendritic cell proliferative disorder, RDD is a monocyte/macrophage proliferative disease.[11] RDD most commonly affects young adults in the first or second decade, although it may present at any age group, as observed in our study. Our relatively older cohort is likely due to referral bias because our institution receives a large referred adult population. There is no particular gender predilection in our study which is similar to previous reports.[3] Our cohort was predominantly Caucasian, which differs from the largest published series which reported a slight predominance in African Americans.[3] Unlike certain proliferative histiocytic disorders like pulmonary LCH, the prevalence of cigarette smoking was very low in the current series, suggesting a lack of association between smoking and RDD.

The most common presenting symptom in the vast majority of patients is painless cervical lymphadenopathy.[1—3,12] Cutaneous manifestations are reported to occur in about 10% of patients, and generally consist of asymptomatic xanthoma-like, yellowish or reddish-brown papules, nodules and plaques which may ulcerate.[3,10] Respiratory tract involvement has been described in less than 3% of the cases in a large review of 423 registry patients and carries a worse prognosis.[3] Pulmonary parenchymal involvement has also been reported in a case report.[13] In the current series, we describe intrathoracic manifestations in 9 out of 21 RDD patients; in 5 patients the intrathoracic involvement was determined based on the presence of mediastinal lymphadenopathy which could not be explained by alternative etiologies, and was associated with confirmatory biopsies of other sites, predominantly enlarged cervical nodes and skin. When considering only individuals with lower respiratory tract involvement, 4 out of 21 patients were affected, representing a higher percentage and also a better prognosis than previously described. Case reports have been published on primary central airway involvement,[9] and pleural involvement.[7] In the current series, one patient had a pleural effusion. However, no endotracheal or endobronchial disease was documented in our study. In the two patients in whom interstitial disease was observed, the radiographic pattern of involvement showed the presence of an interstitial infiltrate in both lungs, greater in the periphery and in the bases. Cystic change and honeycombing were minimal or absent. Prior to surgical lung biopsy, the provisional diagnosis based on imaging findings was consistent with non-specific interstitial pneumonia in one of these cases (see Fig. 2). The 18F-Fluorodeoxyglucose (18FDG) positron emission tomography (PET-CT) scan may demonstrate pathologic uptake in involved organs, and may be useful in documented the extent of disease in patients with RDD, as recently reported.[5,14]

Laboratory testing shows no specific abnormalities in RDD. The diagnosis is made on the basis of characteristic clinical features (particularly the presence of painless adenopathy with or without skin or other manifestations) in combination with characteristic histologic findings in tissue biopsy specimens. There are two cardinal features on histology.[15] The first is the presence of emperipolesis which represents histiocytic phagocytosis of intact lymphocytes, plasma cells, and cellular debris as illustrated in Fig. 3. The second is a characteristic pattern of cell surface receptor expression: positive for S100 protein, CD14, CD68 (macrophage markers), positive for CD11c (early dendritic cell marker), but negative for CD1a (positive on Langerhans-type of dendritic cells) and MHC-2 (generally positive on dendritic cells).[8] Thus the cell of origin of RDD is postulated to be a monocyte-derived cell that is on its way to macrophage differentiation and at the same time has some markers of early dendritic cell phenotype. The background often shows mixed inflammatory infiltrates rich in plasma cells as illustrated in Fig. 3. The differential diagnosis includes atypical chronic infections (mycobacterial or fungal), certain indolent low-grade lymphomas, immunoglobulinG4 (IgG4)-related interstitial lung disease, Erdheim-Chester disease, and Langerhans cell Histiocytosis.[1,2,8,10,16,17] All our patients had biopsy-proven disease mainly from lymphatic nodes; however, three patients were diagnosed based on lung biopsies.

RDD, though a benign disorder, can sometimes behave in an aggressive manner, leading to significant morbidity and mortality. Approximately 50% of patients do not require therapy and spontaneous remissions have been described to occur.[18] Our study showed only few deaths with non-RDD related fatalities. Moreover, the median survival was greater than 5 years after diagnosis, irrespective of extranodal involvement. For patients with progressive or symptomatic presentation, or patients with prominent cosmetic problems due to cutaneous disease, corticosteroids have been widely suggested but their efficacy is unclear.[2,12,15,18—21] Most of the patients described in this study were treated with corticosteroids with adequate response. Surgery, radiation therapy and/or chemotherapy (vinca alkaloids, cladribine, rituximab, 6-mercaptopurine and oral methotrexate) have been considered in patients not adequately controlled with steroid treatment.[5,12,18,22] There are a few case reports describing the use of alpha-

Table 2 Clinical, radiological and therapeutic characteristics of patients with RDD and intrathoracic manifestations.

	Gender	Age (years)[a]	Survival	Site of biopsy	Respiratory symptoms	Non-pulmonary manifestations	Smoking history	PFT	CT findings	Treatment	Outcome
1	Female	2	Alive	Cervical lymph node	- Dyspnea and cough	- Cervical lymphadenopathy	No	Not performed	- Mediastinal lymphadenopathy with mild airway extrinsic compression	- Steroids - Methotrexate - 6-Mercaptopurine - Vinblastine	Improved
2	Female	45	Alive	Cervical lymph node	- Dyspnea - Cough	- Cervical lymphadenopathy	No	Not available	Not available	- Chlorambucil - Steroids	Improved
3	Male	51	Alive	Cervical lymph node	- Dyspnea	- Cervical and abdominal lymphadenopathy - Scotomas	Active 15 pack/year	Normal	- Mediastinal lymphadenopathy - Air trapping	- Steroids	Improved
4	Female	50	Alive	Skin	- Dyspnea - Sore throat - Hoarseness	- Skin changes - Uveitis - Cervical lymphadenopathy	No	Mild obstruction normal DLCO	- Pulmonary cysts lower lung predominant - Bronchiectasis	- No	Not available
5	Male	46	Dead	Mediastinal lymph node	- Dyspnea	- Splenomegaly	Former 10 pack/year	Not available	- Pleural effusion - Mediastinal lymphadenopathy	- Steroids	Improved
6	Female	41	Alive	Lung	- Cough - Wheezing	- None	No	Not available	- Mediastinal lymphadenopathy - Peribronchial lymph node enlargement	- No	Stable
7	Female	21	Alive	Cervical lymph node	- Dyspnea - Cough	- Cervical lymphadenopathy - Nasal congestion	No	Not available	- Mediastinal lymphadenopathy	- Steroids - Interferon-alpha	Improved
8	Male	73	Alive	Lung	- Dyspnea	- Cervical and abdominal lymphadenopathy - Lower extremity edema	No	Not available	- Bilateral interstitial infiltrates - Hilar and mediastinal lymphadenopathy	- Steroids	Improved
9	Male	26	Alive	Lung	- Dyspnea - Cough	- None	No	Moderate Restriction DLCO 33%	- Bilateral interstitial infiltrates	- Steroids	Worsening

PFTs: Pulmonary function test, RDD: Rosai—Dorfman Disease, CT: Computed tomography, DLCO: diffusing capacity of the lung for carbon monoxide.
[a] Age at time of diagnosis.

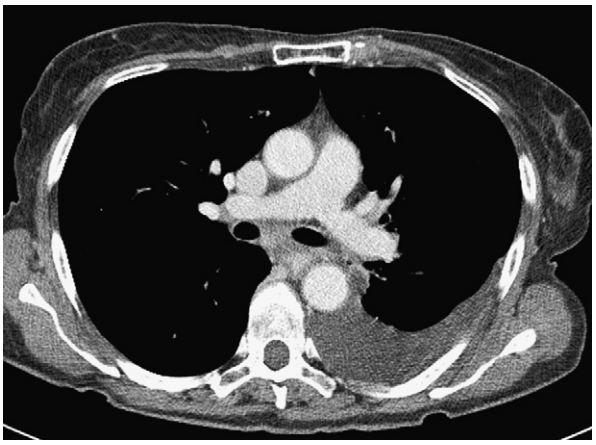

Figure 1 Contrast-enhanced CT of the chest showing left sided pleural effusion and the presence of mediastinal lymphadenopathy in a 46 year-old patient with RDD (patient #5 in Table 2). Diagnosis of RDD was established by mediastinal lymph node biopsy.

interferon.[18,23] One patient in the current series was treated with interferon-alpha. Unfortunately, that patient was lost to follow up.

We acknowledge several limitations in the current study. First, our study has a retrospective observational design with its inherent biases. Complete medical records and follow up were not widely available for all patients. Also, the findings from the current study may reflect regional referral biases particular to our institution and may be difficult to generalize.

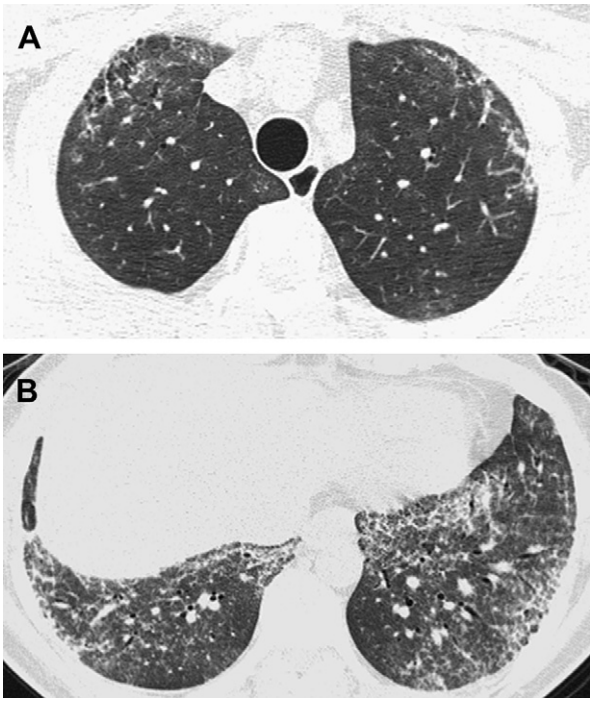

Figure 2 Representative non-enhanced high resolution CT images from the upper (panel A) and lower chest (panel B) in a 26 year-old patient with surgical lung biopsy-proven RDD show bilateral, subpleural reticular opacities, bilateral scattered areas of ground glass attenuation, and mild traction bronchiectasis in the bases. A few tiny cystic lesions are present in the upper lung fields, but no honeycombing was present.

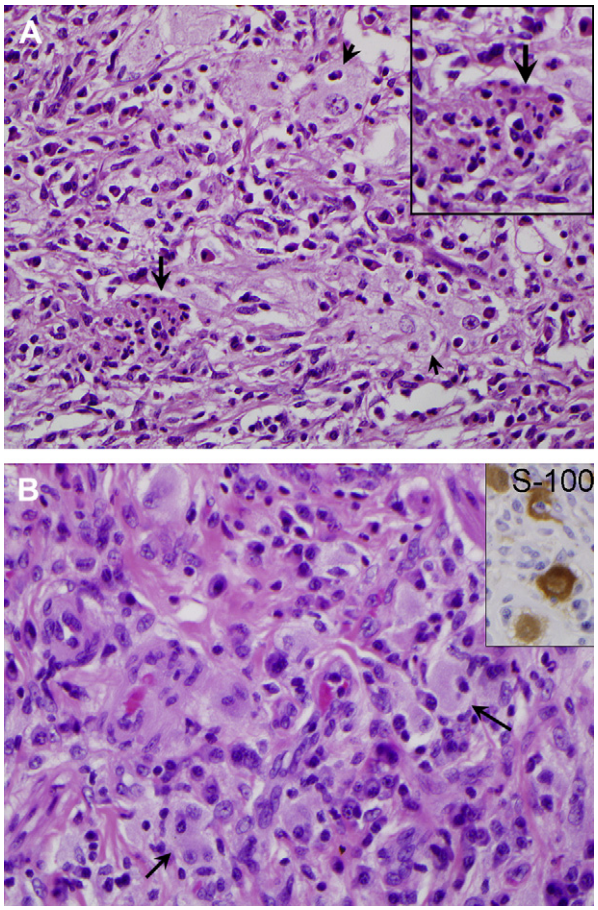

Figure 3 A. Histopathologic findings on surgical lung biopsy (patient #8 in Table 2) demonstrating interstitial thickening due to abnormal histiocytic collections and associated mixed inflammatory infiltrates (hematoxylin eosin staining, 400× original magnification). Arrows point to histiocytic cells engulfing leukocytes (emperipolesis — see insert). B. Histopathologic findings on surgical lung biopsy of a 26 year-old patient with RDD whose CT is shown in Fig. 2. Histiocytes contain intracytoplasmic leukocytes (emperipolesis) (arrows) and are accompanied by mixed inflammatory infiltrates including many plasma cells (hematoxylin and eosin staining, 400× original magnification). Abnormal histiocytes are positive for S100 staining (inset; anti-S100 immunohistochemical staining, 400× original magnification).

Conclusions

Intrathoracic manifestations of RDD are common and include mediastinal lymphadenopathy, airway disease, pleural effusion, cystic and interstitial lung disease. Although limited in size, this series suggests the prognosis of patients with RDD and intrathoracic manifestations is relatively good.

Conflict of interest statement

The authors of this manuscript do not have any relevant financial disclosures and have no conflict of interest to disclose regarding the content of this manuscript.

Acknowledgments

Supported by an American Histiocytosis Association award to RV. The authors have no conflict of interest or any disclosures relevant to this publication. All authors have directly contributed to the content of this manuscript and reviewed the final version.

Rodrigo Cartin-Ceba and Jason M Golbin wrote the manuscript. Eunhee S Yi provided histopathological figures and helped draft all portions of the manuscript dealing with pathology of RDD. Udaya BS Prakash helped with the original study design, reviewed and revised the manuscript. Robert Vassallo edited and prepared the final manuscript, figures, and references.

References

1. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. *Arch Pathol* 1969;**87**:63—70.
2. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a pseudolymphomatous benign disorder. Analysis of 34 cases. *Cancer* 1972;**30**:1174—88.
3. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai—Dorfman disease): review of the entity. *Semin Diagn Pathol* 1990;**7**:19—73.
4. Goodnight JW, Wang MB, Sercarz JA, Fu YS. Extranodal Rosai—Dorfman disease of the head and neck. *Laryngoscope* 1996;**106**:253—6.
5. Konca C, Ozkurt ZN, Deger M, Aki Z, Yagci M. Extranodal multifocal Rosai—Dorfman disease: response to 2-chlorodeoxyadenosine treatment. *Int J Hematol*; 2008.
6. Andriko JA, Morrison A, Colegial CH, Davis BJ, Jones RV. Rosai—Dorfman disease isolated to the central nervous system: a report of 11 cases. *Mod Pathol* 2001;**14**:172—8.
7. Ohori NP, Yu J, Landreneau RJ, Thaete FL, Kane K. Rosai—Dorfman disease of the pleura: a rare extranodal presentation. *Hum Pathol* 2003;**34**:1210—1.
8. Wang CW, Colby TV. Histiocytic lesions and proliferations in the lung. *Semin Diagn Pathol* 2007;**24**:162—82.
9. Carpenter 3rd RJ, Banks PM, McDonald TJ, Sanderson DR. Sinus histiocytosis with massive lymphadenopathy (Rosai—Dorfman disease): report of a case with respiratory tract involvement. *Laryngoscope* 1978;**88**:1963—9.
10. McClain KL, Natkunam Y, Swerdlow SH. Atypical cellular disorders. *Hematology Am Soc Hematol Educ Program*; 2004: 283—96.
11. Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M, et alReclassification Working Group of the Histiocyte Society. Contemporary classification of histiocytic disorders. The WHO Committee on histiocytic/reticulum cell proliferations. *Med Pediatr Oncol* 1997;**29**:157—66.
12. McAlister WH, Herman T, Dehner LP. Sinus histiocytosis with massive lymphadenopathy (Rosai—Dorfman disease). *Pediatr Radiol* 1990;**20**:425—32.
13. Zander MP, Foster RA, Ohori P, Yousem S, Travis WD. Pulmonary parenchymal sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman disease). *Mod Pathol* 1997;**10**:174A.
14. Hida AI, Yagi S, Obase Y, Nishimura H, Akiyama T, Irei I, et al. Rosai—Dorfman disease presenting as a solitary mediastinal mass. *Pathol Int* 2009;**59**:265—8.
15. Chu P, LeBoit PE. Histologic features of cutaneous sinus histiocytosis (Rosai—Dorfman disease): study of cases both with and without systemic involvement. *J Cutan Pathol* 1992;**19**: 201—6.
16. Shigemitsu H, Koss MN. IgG4-related interstitial lung disease: a new and evolving concept. *Curr Opin Pulm Med* 2009;**15**:513—6.
17. Shrestha B, Sekiguchi H, Colby TV, Graziano P, Aubry MC, Smyrk TC, et al. Distinctive pulmonary histopathology with increased IgG4-positive plasma cells in patients with autoimmune pancreatitis: report of 6 and 12 cases with similar histopathology. *Am J Surg Pathol*; 2009.
18. Pulsoni A, Anghel G, Falcucci P, Matera R, Pescarmona E, Ribersani M, et al. Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai—Dorfman disease): report of a case and literature review. *Am J Hematol* 2002;**69**:67—71.
19. Shaver EG, Rebsamen SL, Yachnis AT, Sutton LN. Isolated extranodal intracranial sinus histiocytosis in a 5-year-old boy. Case report. *J Neurosurg* 1993;**79**:769—73.
20. Zagdanska J, Krakowka P, Polowiec Z. [Sinus histiocytosis with generalized lymphadenopathy-Rosai—Dorfman disease]. *Pneumonol Alergol Pol* 1992;**60**:55—62.
21. Wenig BM, Abbondanzo SL, Childers EL, Kapadia SB, Heffner DR. Extranodal sinus histiocytosis with massive lymphadenopathy (Rosai—Dorfman disease) of the head and neck. *Hum Pathol* 1993;**24**:483—92.
22. Pagel JM, Lionberger J, Gopal AK, Sabath DE, Loeb K. Therapeutic use of Rituximab for sinus histiocytosis with massive lymphadenopathy (Rosai—Dorfman disease). *Am J Hematol* 2007;**82**:1121—2.
23. Lohr HF, Godderz W, Wolfe T, Heike M, Knuth A, Meyer zum Buschenfelde KH, et al. Long-term survival in a patient with Rosai—Dorfman disease treated with interferon-alpha. *Eur J Cancer* 1995;**31A**:2427—8.